REMARKS

Claims 12-29 are pending in the application. Claims 1-11 and 30-40 are canceled without prejudice or disclaimer. Claims 12-29 are under active consideration.

The specification has been amended to properly recite trademarks with marks capitalized and accompanied by generic terminology. Entry of the amendment to the specification is respectfully requested.

Claims 12, 17, 22, and 29 have been amended, and claims 1-11 and 30-40 have been canceled without prejudice or disclaimer in order to remove non-elected subject matter. Applicant reserves the right to prosecute non-elected subject matter in subsequent divisional applications.

Claim 12 has been amended to recite "a method for detecting the presence of West Nile virus (WNV) in a biological sample, the method comprising: isolating nucleic acids from a biological sample suspected of containing WNV; amplifying the nucleic acids using a sense and an antisense primer wherein each of the primers is not more than about 60 nucleotides in length and is sufficiently complementary to a portion of the antisense and sense strands, respectively, of the isolated nucleic acid to hybridize therewith to allow amplification of said WNV nucleic acids, and (a) the sense primer comprises SEQ ID NO:34; (b) the antisense primer comprises SEQ ID NO:35; and detecting the presence of the amplified WNV nucleic acids as an indication of the presence of WNV in the sample." Support for the amendment can be found in the original claims and in the specification, for example, at page 3, lines 20-25; page 4, line 19 through page 5, line 8; and page 15, lines 15-28. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claim 17 has been amended to make explicit that the capture nucleic acids selectively bind to WNV nucleic acids from the biological sample. Support for the amendment can be found in the specification, for example, at page 17, lines 6-9; and page 19, lines 11-13. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Applicant has amended claims 20 and 21 to replace the term TaqMan™ with the generic term fluorogenic 5' nuclease assay. Support for the amendment can be found in the original claims and in the specification, for example, at page 29, lines 11-13. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claim 22 has been amended to make explicit that the probe selectively binds to WNV nucleic acids. Support for the amendment can be found in the specification, for example, at page 15, line 29 through page 16, line 12; and page 17, lines 6-9. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Restriction Requirement

Applicant affirms the election with traverse of Group II, which corresponds to claims 12-29 drawn to a method of detecting West Nile virus, and the further election, also with traverse, of SEQ ID NO:8, SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:40, and SEQ ID NO:52. Applicant thanks the Examiner for extending the prior art search to include the sequences of SEQ ID NO:53 and SEQ ID NO:45.

Hyperlinks

The Examiner has objected to the presence of references to hyperlinks and/or other forms of browser-executable code in the specification (Office Action, page 2). Applicant has amended the specification to remove active hyperlinks and therefore respectfully requests that the Examiner withdraw the objection to the specification.

35 U.S.C. § 112, second paragraph

Claims 20-25 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention" (Office Action, page 3). In particular, the Office Action alleges that the trademarked term TaqMan should be capitalized or accompanied by the term ™ or ® symbol wherever it appears and be accompanied by generic terminology (Office Action, page 3). Applicant has amended claims 20 and 21 accordingly to replace the term TaqMan™ with the generic term fluorogenic 5' nuclease assay; therefore, withdrawal of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

35 U.S.C. § 112, first paragraph, Written Description

Claims 12-29 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of an adequate written description. In particular, the Office Action alleges that "[t]he claims do not require that the primers possess any particular distinguishing feature, biologic activity, or conserved structure" (Office Action, page 4). Applicant respectfully traverses the rejection.

In order to comply with the written description requirement, an applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas Cath Inc. v. Mahurkar,* 19 USPQ 1111, 1117 (Fed. Cir. 1991) (cited in MPEP §2163 and in the Examiner Guidelines on Written Description Requirement). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim,* 191 USPQ 90 (CCPA 1976) (cited in MPEP §2163.04 in the Examiner Guidelines on Written Description Requirement). Moreover, it is axiomatic that a patent specification "need not teach, and preferably omits, what is well known in the art." See, *Spectra-Physics, Inc. v. Coherent, Inc.* 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986). Thus, determining whether the written description is satisfied requires

reading the disclosure in light of the knowledge possessed by those skilled in the art. *In re Alton,* 37 USPQ2d 1578 (Fed. Cir. 1996). Applying these tenets, Applicant submits that the Office has failed to carry its burden and that the present claims indeed comply with the written description requirement of 35 U.S.C. §112, first paragraph.

The Office has failed to supply any "evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." *In re Wertheim,* 191 USPQ 90 (CCPA 1976). In fact, a review of the application as a whole, coupled with the knowledge in the art at the time of filing, evidences that the application is more than sufficient to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention. Contrary to the Office's assertions, not only has applicant claimed embodiments expressly called out in the specification, these embodiments are claimed with reference to a particular structure, *i.e.*, the sequences specified in SEQ ID NO:34 and 35. *Fiers v. Revel*, 25 USPQ2d 1661 (Fed. Cir. 1993) clearly states that a chemical structure, such as DNA, may be properly defined by one or more of the parameters "structure, formula, chemical name or physical properties." The claimed genus of oligonucleotides is not "undefined" as alleged (Office Action, page 4). Applicant's claims are framed with reference to concrete sequences and the specification precisely defines those sequences.

With regard to the Examiner's assertion that the primers are not required to possess any particular distinguishing feature and are defined only by sequence identity (Office Action, page 4), Applicant submits that the oligonucleotides, as currently claimed, comply with the written description requirement. Claim 12 recites that the primer sequences are "sufficiently complementary to a portion of the antisense and sense strands, respectively, of the isolated nucleic acid to hybridize therewith to allow amplification of said WNV nucleic acids." Thus, the primers, recited in the claims as currently pending, are limited to those oligonucleotides that have priming function for WNV nucleic acids. In addition, the capture nucleic acids, recited in claim 17, are limited to those oligonucleotides that selectively bind to WNV nucleic acids in a

biological sample. The probe oligonucleotides, recited in claim 22, are limited to those oligonucleotides that selectively bind to WNV nucleic acids.

Furthermore, Applicant sees no reason to unduly limit the claims to the use of the primer, probe and capture oligonucleotides consisting of the sequences of SEQ ID NOS:8, 34, 35, 40, 45, 52, and 53 per se. It is well-known that hybridization can occur even in the presence of extraneous sequences and with oligonucleotides containing as few as 10 contiguous nucleotides that are complementary to the target nucleic acid. Applicant has indeed provided a common attribute (particular sequences) and characteristic (ability to hybridize or selectively bind to a target WNV nucleic acid), such that the claims and application are believed to comply with the written description requirement of 35 U.S.C. §112, first paragraph.

Finally, with respect to the percent identity language, although such language is believed to be fully supported in the application as filed, the recitation of percent identity has been eliminated from the claims.

It is readily apparent that one of skill in the art would recognize that applicant was in possession of the claimed invention at the time the application was filed. Withdrawal of this basis for rejection is therefore respectfully requested.

35 U.S.C. § 103

A. Lanciotti 1 and Lanciotti 2 in view of Buck

Claims 12, 17, and 20-25 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Lanciotti (J. Clin. Microbiol. (2000) 38:4066-4071; hereinafter "Lanciotti 1") and Lanciotti (Science (1999) 286:2333-2337; hereinafter "Lanciotti 2") in view of Buck (BioTechniques (1999) 27:528-536; hereinafter "Buck"). Lanciotti 1 is cited for teaching a method of amplifying and detecting WNV in a sample using a Taqman assay (p. 4066) and a RT-PCR assay. Lanciotti 2 is cited for teaching the complete nucleotide sequence of one of the viral isolates of the WNV genome (p. 2334). Buck is cited for allegedly teaching the use of primers and combinations of primers for use in assays; however, Applicant notes that

Buck pertains to primers for use in DNA sequencing. In particular, the Office Action alleges:

> Since the claimed primers simply represent structural homologs of the oligonucleotides taught by Lanciotti 2, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations. (Office Action, page 7.)

The Office Action further alleges that Buck provides evidence of the equivalence of primers:

> ... Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. (Office Action, page 8.)

Applicant respectfully traverses the rejection under 35 U.S.C. § 103 on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

Applicant submits that the cited references do not disclose or suggest all the limitations of the present invention. Thus, a *prima facie* case of obviousness has not been presented by the Office, and the cited combination is based on impermissible hindsight reconstruction.

None of the cited art, either alone or in combination, teaches or suggests the particular combination of the use of a sense primer not more than about 60 nucleotides in length comprising the nucleotide sequence of SEQ ID NO:34 and an anti-sense primer not more than about 60 nucleotides in length comprising the nucleotide sequence of SEQ ID NO:35, as recited in rejected claim 12. Nor does any of the cited art teach or suggest the use of a capture nucleic acid not more than about 60 nucleotides in length and comprising at least 10 contiguous nucleotides from the sequence of SEQ ID NO:8 or 45, as recited in rejected claim 17 or a probe not more than 60 nucleotides in length

comprising the nucleotide sequence of SEQ ID NO:52 or SEQ ID NO:53, as recited in rejected claim 22.

The Examiner acknowledges that Lanciotti 1 does not specifically teach or suggest any of the oligonucleotides comprising the sequences of SEQ ID NOS:8, 17, 34, 35, 40, 45, 52, or 53, recited in the claims (see Office Action, page 7). Nor does Lanciotti 2 teach or suggest any of the oligonucleotides of the instant invention. Rather, Lanciotti 2 describes sequencing of genomic RNA from the WNV isolate NY99. Lanciotti 2 does not describe or suggest oligonucleotide primers, probes, or capture nucleic acids for use in diagnostic assays for detection of virus as disclosed in the instant application.

The secondary reference of Buck is completely irrelevant. Nowhere does Buck even mention WNV. Buck pertains to strategies for selecting primers for **DNA sequencing**. Accordingly, Buck describes the performance of primers with regard to sequencing (*e.g.*, the length of sequence generated, number of errors in sequence). Notably absent is any discussion of the performance of PCR primers with regard to detection of virus in a biological sample. In particular, Buck fails to discuss how primer selection affects the level of amplification of nucleic acids. Nor does Buck describe or suggest the use of labeled probes for detection, or the use of capture nucleic acids for isolating target nucleic acids.

Contrary to the Examiner's assertions (see Office Action, page 8), not all primers are equivalent for detection of virus. For example, primers can be carefully selected to avoid detection of viruses other than WNV, to selectively detect a single viral strain, or to detect multiple viral strains. The selection of primers determines what viruses are detected and with what sensitivity and specificity.

In the instant application, the specification describes in particular, the selection of conserved sequences of the WNV genome for use in primers, probes, and capture nucleic acids. See specification, for example, at page 19, lines 13-25; page 20, lines 1-10; page 29, lines 11-15; and Example 2. The use of conserved sequences allows for the detection of different strain variants of WNV. None of the cited references describes or suggests the selection of the particular conserved sequences used in the instant invention for

detection of WNV. Lanciotti 1 fails to describe or suggest using primers derived from conserved regions of the WNV genome, and in fact, states that primers were designed to specifically detect the NY99 strain (see page 4066, col. 2). Notably, the primers tested by Lanciotti et al. were not found to be equivalent (see page 4070). One set of primers was selective for the NY99N strain; another amplified every WNV strain that was tested. Obviously, selecting primers capable of detecting multiple viral strains was not a concern for nucleic acid sequencing as described by Lanciotti 2 and Buck. Again, none of the cited references disclose or suggest any of the primers, probes, or capture nucleic acids of the instant invention. Therefore, no combination of the references discloses or suggests all the limitations of claims 12, 17, and 20-25.

B. Lanciotti 1 and Lanciotti 2 in view of Buck, and further in view of Bhatt

In addition, claims 12-17 and 20-25 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Lanciotti 1 and Lanciotti 2 in view of Buck and further in view of Bhatt et al. (Nucleosides & Nucleotides (1999) 18:1297-1299); hereinafter "Bhatt"). Bhatt is cited for teaching a solid support with magnetic beads and capture nucleic acids attached for hybridization to complementary target nucleic acid sequences in a biological sample (p. 1297). In particular, the Office Action alleges:

> One or ordinary skill in the art at the time the invention was made would have had a motivation to combine the TaqMan/RT-PCR methods of amplification and detection of Lanciotti 1 and Lanciotti 2 in view of Buck et al. with the isolation step of Bhatt et al. because Bhatt et al. teaches that capturing the target DNA on particles and separating it from non-specific DNA dramatically reduces background for enhanced specificity (p. 1297). (Office Action, page 10.)

Applicant respectfully traverses the rejection under 35 U.S.C. § 103 on the following grounds.

As stated previously, the combination of Lanciotti 1, Lanciotti 2, and Buck fails to teach or suggest methods for detecting the presence of WNV in a biological sample using the primers, probes, and capture nucleic acids of the instant invention. Bhatt fails to fill the gaps. Bhatt pertains to detection of nucleic acids by cycling probe technology, which

is described as not requiring target amplification. Thus, Bhatt does not describe or suggest or provide any motivation for using the primers or methods of nucleic acid amplification of the instant invention. Nor does Bhatt describe any of the capture nucleic acids recited in the claims. Therefore, no combination of the references discloses or suggests all the limitations of claims 12, 17, and 20-25.

C. Lanciotti 1 and Lanciotti 2 in view of Buck and Bhatt, and further in view of Suzuki

Claims 18 and 19 have also been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Lanciotti 1 and Lanciotti 2 in view of Buck and Bhatt and further in view of Suzuki et al. (J. Virol. Meth. (1995) 55:347-356; hereinafter "Suzuki"). Suzuki is cited for teaching a reverse transcriptase assay for virus detection incorporating labeled dUTP onto oligo-dT primers that are hybridized to polyA templates (p. 347). In particular, the Office Action alleges:

> One of ordinary skill in the art at the time the invention was made would have been motivated to combine the TaqMan/RT-PCR methods of amplification and detection of Lanciotti 1 and Lanciotti 2 in view of Buck et al. with the poly-A chains of Suzuki et al. because Suzuki et al. teaches that attaching oligonucleotide primers to polyA templates increased the efficiency of capture of the labeled nucleotide compared to the solution phase format and eliminated a transfer step to improve use and assay reproducibility (p. 355). (Office Action, page 11.)

Applicant respectfully traverses the rejection under 35 U.S.C. § 103 on the following grounds.

The secondary reference of Suzuki also fails to teach or suggest the claimed methods of WNV detection. Suzuki pertains to methods of detecting HIV infection by assaying for reverse transcriptase activity. Nowhere does Suzuki mention isolating target nucleic acids from cells by using capture nucleic acids of any kind, nor any method of nucleic acid amplification. Rather, Suzuki is about detection of reverse transcriptase activity in infected cells using an enzymatic assay. Suzuki uses the polyA template as a general substrate for reverse transcriptase. Activity is detected by the incorporation of biotin-labeled dUTP, which binds streptavidin conjugated to horseradish peroxidase. Thus, Suzuki describes a colorimetric assay for reverse transcriptase, which has nothing

to do with detection of viral nucleic acids. Therefore, Suzuki provides no motivation or suggestion to use the capture nucleic acids of the instant invention attached to a homopolymer chain, as recited in claims 18 and 19.

D. Lanciotti 1 and Lanciotti 2 in view of Buck, Bhatt, and Suzuki, and further in view of King

Claims 26-29 have also been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the references of Lanciotti 1 and Lanciotti 2 in view of Buck, Bhatt, and Suzuki, and further in view of King et al.(J. Virol. Meth. (2003) 107:53-61; hereinafter "King"). King is cited for teaching a TaqMan assay for African swine fever virus detection incorporating an internal control plasmid. In particular, the Office Action alleges:

> One of ordinary skill in the art at the time the invention was made would have been motivated to combine the TaqMan/RT-PCR methods of amplification and detection of Lanciotti 1 and Lanciotti 2 in view of Buck et al., Bhatt et al. and Suzuki et al. with the internal control sequence of King et al. because King et al. teaches the use of an internal control sequence to use as a positive control for the reverse transcription or amplification steps (p. 54). King also teaches the use of detectably labeled probes (p. 57). (Office Action, pages 12-13.)

Applicant respectfully traverses the rejection under 35 U.S.C. § 103 on the following grounds.

King also fails to fill the gaps. King discloses a TaqMan PCR assay for detection of African swine fever virus. King fails to describe any of the primers, capture nucleic acids, or probes recited in the claims. Nor does King describe or suggest the particular internal control sequence comprising the nucleotide sequence of SEQ ID NO:17, recited in claim 27. As discussed above, none of the other references describe or suggest the oligonucleotides used in the claimed methods of WNV detection. Therefore, no combination of the references discloses or suggests all the limitations of claims 26-29.

E. No Motivation to Combine the Teachings of the Cited References

Virtually all inventions are combinations of elements that can be individually identified in multiple references. However, the mere identification in a reference of

individual components of claimed limitations cannot be a basis for an obviousness rejection. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000).

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicant invites the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

Marcella Lillis, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

Respectfully submitted,

Date: March 21, 2006

By: Jenny Buchbinder

Jenny Buchbinder, Ph.D.
Registration No. 48,588
(650) 354-3383

CHIRON CORPORATION
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662-8097